Science and Medical Affairs **Quality & Compliance** **POLICY**	sanofi aventis Because health matters
Quality Document ID: WW-QUAL-CQC-POL-0001 **Version Number: 01**	**Effective Date:** **01-JUN-2006**

Scientific Misconduct – Serious GCP Non-Compliance

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Table of Contents

1. PURPOSE

To describe sanofi-aventis policies and general principles on the course of action, which must be followed if any activities occurring during the course of a clinical trial sponsored by sanofi-aventis or its affiliates are suspected of scientific misconduct / serious GCP non-compliance.

To ensure that all cases of suspected scientific misconduct / serious GCP non-compliance are investigated, documented and reported appropriately.

2. APPLICABLE TO

Sanofi-aventis and its affiliates:

- Affiliate Medical Affairs
- Affiliate Medical Direction
- Affiliate Quality Assurance (QA)
- Affiliate Pharmacovigilance
- Clinical Research Unit (CRU)
- Affiliate Regulatory Affairs

Science & Medical Affairs (SMA):

- Clinical Quality & Compliance (CQ&C)
- International Clinical Development (ICD)
- Global Medical Affairs (GMA)
- Corporate Regulatory Affairs (CRA)
- Global Pharmacovigilance & Epidemiology (GPE)
- Legal (as appropriate)
- Any other Corporate or Affiliate function as relevant depending on particular situation (e.g., Global Preclinical Development, Project Direction, Purchasing, Human Resources)

3. WORKING REQUIREMENTS

3.1. Each entity of sanofi-aventis sponsoring clinical trials should ensure that they implement systematic measures to prevent, detect, investigate and manage non-compliance so that GCP Principles and Local Regulations be implemented and followed at any stage of a clinical trial. This includes regular monitoring of the conduct of clinical trials as well as means to detect and report serious deviations / violations when these are of a nature and significance which may affect the safety and rights of human subjects and/or the integrity of the data generated.

3.2. It is the responsibility of all individuals involved in the conduct of or the handling of data from any sanofi-aventis sponsored clinical trial, to be alert to the possibility of scientific misconduct / serious GCP non-compliance

3.3. Any case of suspected scientific misconduct / serious GCP non-compliance should be subject to prompt review and follow-up by a designated Investigation Panel.

3.4. The investigation panel will be normally chaired by a senior QA / CQ&C representative and be composed of key function representatives from field operational and management levels, affiliate and corporate as appropriate, including Clinical, Regulatory Affairs, and other functions as appropriate i.e. Pharmacovigilance, Legal, Human Resources, etc.

These representatives should be of a level of seniority allowing them to make rational and justified proposals for an action plan regarding the conduct of the investigation and management of the various aspects potentially impacted by the non-compliance.

They should ensure that the information remains at the appropriate level of confidentiality and report to their management on developments with the investigations and action plans.

3.5. Investigation Panel will determine methodology, scope, and timelines for follow-up investigation and actions to be taken if any regarding remediation, data handling and / or notification of Health Authorities / IEC as required.

3.6. All steps of investigation should be documented so that all decisions and actions can be reconstructed from the documentation and be subject to audit and/or inspection.

3.7. In the case of disagreement between members of the Investigation Panel on actions to be taken, the matter will be forwarded to SMA CQ&C senior management and appropriate Senior Management for arbitration.

3.8. All documentation related to a particular function (i.e. monitoring visit reports, minutes of clinical meetings, contact reports) will remain the responsibility of each function for filing and archiving. However, documentation copied or collected to support the investigation (i.e. audit reports, investigation panel meeting minutes) will remain the responsibility of QA / CQ&C for filing and archiving.

3.9. All communication regarding cases of scientific misconduct / serious GCP non-compliance should be kept strictly confidential and avoid undue reference to particular individuals unless deemed necessary.

3.10. QA / CQ&C should strictly control communication of Investigation results outside of the company. No audit report or related documentation will be submitted to an external body unless formally requested and approved by the Investigation Panel.

3.11. In the case CROs or Partners are taking part in a development project/trial in a study sponsored by sanofi-aventis, legal clauses should be secured in the contract to cover

the management of scientific misconduct / serious GCP non-compliance and obligation of parties in accordance with the responsibilities of sanofi-aventis as a sponsor.

This should include:

- Obligation to report any scientific misconduct / serious GCP non-compliance as part of the operations performed in an appropriate timeframe and conduct proper investigations and follow-up / corrective actions in agreement with the sponsor and as part of the CRO / Partner quality system.
- Obligation to inform the sponsor promptly in case of any regulatory action by a Health Authority and provide documentation covering activities being part of the agreement.

4. RESPONSIBILITIES

4.1 Internal reporting of suspected scientific misconduct / serious GCP non-compliance

The individual who is informed from any source (internal and / or external) or discovers the suspected scientific misconduct / serious GCP non-compliance must promptly inform their functional manager (ICTM for ICD clinical trials) and their line manager of the suspicion.

The line manager is responsible for promptly reviewing the available elements of information or documentation.

If it is determined by the line manager that there is any reasonable possibility of scientific misconduct / serious GCP non-compliance, all pieces of evidence and documentation of the specific case should be collected. If possible provide photocopies or example of the source data / information under suspicion.

The line manager should ensure prompt communication of relevant information to QA for local clinical trials and CQ&C for ICD and GMA clinical trials.

QA / CQ&C will review the available elements of information with key personnel to determine the need to convene an investigation panel.

4.2 Suspected scientific misconduct / serious GCP non-compliance – constitution of an Investigation Panel

QA / CQ&C will promptly identify the list of core members and initiate the investigation panel if required. Other ad hoc members may be added as investigation proceeds.

The investigation panel will meet as required for a timely management of the case. It is responsible for the overall supervision of the management of the case, which includes:

- Review and analysis of the evidence for a suspected scientific misconduct / serious GCP non-compliance,
- Decisions on how to proceed with further investigations if deemed necessary,
- Monitoring of the progress made with the investigation,

- Decisions on actions to be taken as a consequence of the results of the investigations,
- Ensuring proper documentation of key steps,
- Identifying potential preventive actions to avoid recurrence of similar situations and conveying them to the appropriate responsible departments for further action.

If an investigation is not required then the reasons for this decision will be documented in a confidential memo to be maintained by QA / CQ&C in the files.

4.3 Conduct of further investigations to confirm scientific misconduct / serious GCP non-compliance

Any scientific misconduct / serious GCP non-compliance should be the object of an analysis of the impact to determine the potential risks on:

- The subjects safety and their rights,
- The integrity of the data generated,
- Other risks to be anticipated,
- Potential impact on other studies sponsored by sanofi-aventis and performed at the same investigational site (e.g. involving R&D trials and post-marketing trials)

For scientific misconduct / serious GCP non-compliance at an investigational site, temporary suspension of recruitment and/or subjects treatment or follow-up should be considered promptly. This involves written notification of the Principal Investigator, suspension of Investigational Products (IP) shipment to the site and notification of the Ethics Committee/IRB.

Investigations will be conducted according to a plan designed by the Investigation Panel (action, responsible person(s) and timing) and may include (depending on the specific situation):

- Further monitoring visit(s) to gain additional data or evidence

Note: At this stage, monitoring team should be instructed to take all relevant copies from documentation available at the site substantiating evidence of non-compliance with appropriate precautions to subjects data protection (confidentiality).

- Internal review of documentation available internally to gather and analyze all elements of information (e.g. monitoring records and assessment of site compliance as reported in monitoring visit reports, correspondence with the site and essential documents).
- For-cause audit to be performed by QA / CQ&C in the appropriate timeframe.

Note: in instances where extensive documentation and review is available from operational staff, an audit may not be necessary. The decision to perform an audit will be made by QA / CQ&C Responsible person in liaison with CQ&C management.

4.4 Actions to be considered if scientific misconduct / serious GCP non-compliance is confirmed

Upon results of investigation and confirmation of serious GCP non-compliance, decisions should be considered by the Investigation Panel and approved by Management. These decisions concern the following areas (depending on the specific situation).

4.4.1 Premature site / trial subjects discontinuation

- permanent hold on patients recruitment,
- discontinuation of treatment / follow-up for subjects on treatment,
- retrieval of IPs from the site,
- site closure,
- suspension of payments.

4.4.2 Notification to Health Authority (CA)

A written notification is prepared by Regulatory Affairs representative in liaison with the Investigation Panel and submitted by Regulatory Affairs in compliance with the relevant submission procedures.

Note: In the case of scientific misconduct in a site outside of the USA for an IND study, the FDA must be informed.

4.4.3 Notification to IEC / IRB by Clinical Representative – To be prepared in parallel and consistent with notification to CA

A written notification is prepared by the responsible Clinical person in liaison with the Investigation Panel. This should be performed in parallel with notification to CA and on the same basis of information.

If the trial organization includes a Steering Committee or other Committees, communication of information to these Committees be should be considered. This is the responsibility of the Clinical person supervising the trial.

4.4.4 Use of data from the centre for statistical analysis (safety, efficacy)

Taking into consideration the impact of the non-compliance on the data integrity and the design of the trial, the Investigation Panel should determine:

- whether the data could be usable or not,
- the timeframe for the decision on the way to handle data in the final analysis

All data, whatever their degree of credibility, must be presented in the Clinical Study Report (CSR). Criteria for excluding data from the statistical analysis should be justified and this should be reflected in the Statistical Analysis Plan (SAP) and the CSR. If the integrity of the data proves to be compromised, these data should normally be excluded from the study analysis except when justified scientifically and ethically.

4.4.5 Statement in Clinical Study Report

An appropriate statement regarding the scientific misconduct / serious GCP non-compliance must be included in the CSR.

This statement would typically include information describing the site(s) and subject(s) involved, the general nature of the deficiencies and action taken (i.e. prior CA notification, analysis impact).

4.4.6 Notification to other Official bodies (e.g. Medical Council) depending on country rules / recommendations for disciplinary action).

5. RELATED DOCUMENTS

NONE

6. DEFINITIONS

Refer to Q&C Clinical Domain Glossary for additional definitions.

7. ABBREVIATIONS

Abbreviation	Description
CQ&C	Clinical Quality and Compliance
CRO	Contract Research Organization
QA	Quality Assurance
SMA	Science and Medical Affairs

8. APPENDICES

Appendix 1: Template for Investigation Panel Meeting Minutes

Appendix 2: Composition of Investigation Panel and Standard distribution list for Investigation Panel Meeting Minutes

Appendix 3: Methods for detection of Scientific Misconduct / Serious GCP Non-Compliance

Appendix 4: Document History

Appendix 1: INVESTIGATION PANEL MEETING MINUTES TEMPLATE

From :

To : **CC :**

Date :

Subject : Study Code / investigator identification
Review of a case of Scientific Misconduct – Serious GCP non-compliance
Meeting dated DD MMM YYYY / Minutes

Participants:

Investigation Panel Members (please clearly mention present or excused)

This meeting was conducted to XXXXXXXx and decide on further actions about this case as per aventis-sanofi Policy _____.

Study / Site Information and Status

To be completed if applicable i.e. case investigated is associated with a study and a site.

Background

Provide background for feedback on the case being investigated (date reported, how, pieces of information / documents collected / copied, etc.).

Case Review and Agreed Action Steps and Investigation Plan

State the elements reviewed, the agreement reached, methodology and scope of the investigation (if further investigated) and Investigation plan according to the agreements reached during the meeting.

Status of investigation and action plan

e.g. state when investigation is *in progress* and state when completed and considered *closed*

Example for the composition of an investigation panel investigating on a case of alleged scientific misconduct / serious GCP non-compliance detected in an investigating site for a clinical trial performed by International Clinical Development (ICD) and monitored by Clinical Research Unit (CRU)

Appendix 2: COMPOSITION OF THE INVESTIGATION PANEL and STANDARD DISTRIBUTION LIST FOR INVESTIGATION PANEL MEETING MINUTES

	TO Members of Investigation Panel	CC (for Information)
Minutes	Direct addressees include all the members who compose the investigation panel QA / CQ&C Responsible Person (if not the author of the minutes) Corporate CTT members: ICTM, CSD, other as relevant Head of CRU or delegate Other members of the CRU ad hoc upon decision of Head of CRU (e.g. Project Leader, CRA) Corporate Regulatory Affairs representative Clinical Research Director and GCPM (as relevant) Pharmacovigilance Representative (Corporate and Affiliate as relevant) Affiliate Regulatory Affairs representative (as relevant) Legal Advisor (Corporate or Affiliate, as relevant)	Information is directed up the following level of Management i.e. Senior Functional Management of all members of Investigation Panel : C Q&C Management C Q&C International Expert Area Affiliate : • QA Management (as relevant) • CRU Head (if delegate part of the investigation panel) • Medical Director • Head of Regulatory Affairs • Legal (as relevant) • Other Dept Heads (as relevant) Corporate / SMA : • Head of Procedures, Training & Information Sharing • Up to Head of Clinical Investigations / Clinical Operations in ICD which includes all intermediate management levels (e.g. TDH, GTOD, CRU Network Leader and Direction) • Head of Regulatory Development / Corporate Regulatory Affairs • Head of Clinical Purchasing Department (as relevant, e.g. if CRO involved) • Head of GPE (as relevant) • Other Department / Function Management (as relevant)

Appendix 3: METHODS FOR DETECTION OF SCIENTIFIC MISCONDUCT

Some methods that may be utilized in detecting these situations include:

- Systematic review of original source records
- Accounting for all records
- Determining if results unexpectedly favor the product under investigation
- Assessing whether the subject inclusion rate matches with the patient population potential of the center
- Identifying if some documents are systematically missing (e.g. lab reports)
- Checking for repeated data patterns
- Checking whether Informed Consent Forms have similar subject signatures
- Checking for problem trends in information capture
- Checking for the sudden appearance of documents which had previously been reported lost
- Identifying record entries and alterations to records which are without plausible explanation
- Assessing whether signatures on source documents are consistent with the signatures log for the site
- Interaction with all study related personnel to confirm their awareness and contribution to the trial

Appendix 4: Document History

Version	Effective Date	Section	Description of Changes
01	01-JUN-2006	ALL	This is the first version of this Policy keeping heritage from Sanofi-Synthelabo and Aventis Pharma.

End of Document